Remarks

Claims 1-13 and 23-28 were pending in the above-captioned application. Claims 2 and 6 have been amended to more particularly point out and distinctly claim that which Applicants consider to be their invention. Responsive to the restriction requirement claims 7 and 8 have been cancelled with traverse and without prejudice.

Upon entry of the above-made amendments, therefore, claims 1-6, 9-13 and 23-28 will be pending in the current application. A copy of the claims marked up showing the amendments, as well as a clean copy of the claims encompassing the amendments, is attached hereto.

The amended claims are fully supported in the specification as originally filed. The amendments, to the Specification and Claims do not add new matter. Applicants respectively request that the amendments be entered. A copy of the specification marked up showing the amendments, as well as a clean copy of the specification encompassing the amendments, is attached hereto.

The following remarks, in conjunction with the above amendments, are believed to be fully responsive to the Official Action.

THE REJECTION UNDER 35 U.S.C. § 112, SECOND PARAGRAPH SHOULD BE WITHDRAWN

In the application, claims 1, 2, 6, 9 and 12-13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite. In particular, the Examiner has objected to several terms in phrases recited in the above-identified claims. In response, Applicants submit that each of these rejections has been overcome and/or obviated, as discussed in detail below.

First, the Examiner has rejected claim 1 for being indefinite because the phrase "contrast generating species" is allegedly being vague and indefinite. In response, Applicants submit that the recited term is clear and definite. Applicants respectfully directs Examiner's attention to page 21, lines 25-33 of the specification, which recites the particulate material in claim 1 comprises at least one chemical entity which is a matrix or membrane and at least one other which is a contrast generating specie. It is well known to a person of ordinary skill in the art a contrast generating specie is a chemical entity that generates a contrast effect when the particulate material is administered to a body. It is also well known to a person skilled in the art which chemical entities generate a contrast effect when different imaging modalities are used. Specifically, definitions are given in the specification for contrast generating species for ultrasound imaging (see page 22, lines 32 to 36), contrast generating species for MR imaging (page 28, line 26 to page 29, line 24), contrast generating species for X-ray imaging (page 30, line 25 to page 31, line

8) and contrast generating species for nuclear medicine contrast agents (page 31, lines 12 to 19). Thus, the phrase "contrast generating species" is clear and definite.

Next, the Examiner contends claim 2 is indefinite because of the phrase "carbon dioxide tension" recited in the claim. In response, Applicants submit the term is an equivalent to carbon dioxide partial pressure. The term "tension" is well known to person skilled in the art. For example, "Dorland's Illustrated Medical Dictionary" (Twenty-sixth Edition) provides that tension is "the partial pressure of a gas in a fluid, e.g., of oxygen in blood". Thus, the term is clear and definite.

Further, the Examiner contends the phrase "tissue diffusion" is vague and indefinite. In response, Applicants submit that it is typographical error. Claim 2 has been amended to recite "tissue water diffusion". The amended term in claim 2 is thus clear and definite.

Next, the Examiner contends that claim 6 uses improper Markush groups. In response, claim 6 has been amended to use proper Markush groups.

The Examiner has further rejected claim 9 because the phrase "in combination with" is allegedly vague and indefinite. In response, Applicants submit that although this term is not further defined in the specification, it is obvious to one skilled in the art that the targeting ligand must be associated with the particulate material, i.e., the targeting ligand and the particulate material must not separate upon administration (otherwise the

particulate material is not directed to the target). To achieve association, covalent binding is preferred, but one skilled in the art could also think of a composition of the particulate material and the targeting ligand. Thus, the term is clear and definite.

The Examiner also rejected claim 12 as indefinite for using the term "sensitive" in the phrase "temperature or pH sensitive liposome". In response, Applicants submit this phrase is well established in the art. In fact, Ozer et al., ("Temperature- and pH-Sensitive Liposomes") was cited by the Examiner herself as prior art for 103(a) rejection (see below).

Next, the Examiner contends that the terms "stable" and "normal" in claim 13 are relative terms and thus indefinite. In response, Applicants again would like to point out that the terms are well known in the art (See Ozer et al., Summary, "these liposomes are designed to be stable up to 37°C"). In addition, the claim itself defines "unstable" as "exhibiting increased water permeability or leakage", thus providing an indirect definition of "stable". This is further disclosed in the specification. Applicants respectfully direct Examiner's attention to page 32, lines 23-30. It discloses that liposomes are stable up to 37°C (normal body temperature as known to one skilled in the art), whereas they exhibit increased water permeability and/or leak as they pass through an area of body in which the temperature is raised (not normal body temperature) as a result of a disease or external heating. Therefore, the rejection should be withdrawn.

Finally, the Examiner contends that the phrase "water permeability or leakage" in claim 13 is vague, as it is not clear how the phrases "permeable" and "leaking" are differentiated. In response, Applicants respectively directs Examiner's attention to page 32, lines 7-13 of the specification. It discloses that a change of contrast may occur due to an increased permeability of the matrix material (namely, increased rate of water transport across the matrix material) even if the agent itself does not leave the matrix (thus no leakage of the agent) as a result of a disease or external heating. Thus, the terms "permeable" and "leaking" are different. An increased permeability does not necessarily mean leakage.

For all the above reasons, Applicants respectfully submit that each of the Examiner's rejections under 35 U.S.C. § 112, second paragraph has been overcome and/or obviated. Applicants therefore respectfully request that the rejections be withdrawn.

THE REJECTION UNDER 35 U.S.C. § 103(a)

SHOULD BE WITHDRAWN

Claims 1-6, 9-13 and 23-28 are rejected under 35 U.S.C. § 103(a) as being obvious over U.S. Pat. No. 6,315,981 ("Unger I") in view of Ozer et al., Ep. Jn. Of Phar. And Biopharm ("Ozer"), or U.S. Pat. No. 5,631,141 ("Sonek"), in further view of U.S. Pat. No. 6,143,276 ("Unger II"). In response, Applicants submit that each of these rejections should be withdrawn for the reasons stated below.

Unger I discloses a contrast medium for MRI, said medium comprises stabilized gas filled microspheres or stabilized microspheres filled with a gaseous precursor (column 4, line 66 to column 5, line 5). In the case of gaseous precursors, said precursors may be temperature activated, resulting in a change from liquid to gas (column 5, lines 8 to 15). The microspheres optionally contain paramagnetic contrast agents (column 5, lines 23-25). The microspheres are formed from a matrix of stabilizing compounds, said matrix retains size and shape for the period of time required to be useful in magnetic imaging (column 7, lines 17 to 23). As further described, the microspheres are resistant to the loss of microsphere structure or encapsulated gas or gaseous precursor for a useful period of time (column 12, lines 33-35). Thus, Unger I discloses an invention where not the microsphere matrix but the gaseous precursor inside the microsphere is responsive to temperature. In contrary thereto, the present invention discloses a particulate material comprising a matrix and a contrast generating species, wherein the matrix is responsive to a pre-selected parameter, e.g. temperature. Unger I teaches away from a matrix which is responsive to temperature. In column 35, lines 40 to 44, it states that the methods of the invention are carried out below the gel state to liquid crystalline state phase transition temperature of the lipid employed (as a matrix). The present invention, on the other hand, discloses that this phase transition temperature is used to design temperature sensitive liposomes which show increased permeability at this phase transition temperature (see specification, page 32, lines 14-30).

Ozer discloses temperature and pH-sensitive liposomes loaded with drugs which leak at the phase transition temperature of their membrane liquids, thus releasing the enclosed drugs.

Obviousness can only be established by combining and/or modifying the teachings of prior art to produce the claimed invention where is some teaching, suggestion or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). A person skilled in the art would not combine the teachings of Unger I and Ozer, because a stable microsphere matrix is a prerequisite of the teaching of Unger I, and the breakdown of the liposome matrix is a prerequisite of the teaching of Ozer. As Unger I teaches away from Ozer, a person skilled in the art would not combine both teachings expecting reasonable success. Thus, the present invention is not obvious in view of Unger I and Ozer.

Sonek discloses biosensors for microthermometry. The biosensors comprise a spherical vesicle comprising a membrane which is impregnated with a dopant that varies its optical emission spectrum as a function of the environmental temperature (column 2, lines 18 to 26). The membrane undergoes a phase transformation between a gel state and a liquid crystal state. In contrary to the present invention, Sonek does not disclose contrast generating species. Moreover, the method according to Sonek requires the

biosensor to be placed inside the body (e.g. via catheters, column 3, line 28), whereas the method according to the instant invention is a non-invasive method.

A person skilled in the art would not combine the teachings of Unger I and Sonek because of the same reasons as stated above, namely, a stable microsphere matrix is a prerequisite of the teaching of Unger I and the breakdown of the liposome matrix is a prerequisite of the teaching of Sonek. Thus, the present invention is not obvious in view of Unger I and Sonek.

Unger II discloses methods which take advantage of the presence of elevated body temperature at a site of, for example, disease or infection. At this site of elevated body temperature, gaseous precursors within a composition comprise bioactive agents, for example, a contrast agent, said gaseous precursors and optionally a stabilizing material, for example, in the form of a vesicle, undergo phase transition to gas (column 1, lines 58 to 61 and column 2, lines 18 to 20). Thus, bioactive agents are released (column 9, lines 17 to 21). In contrary thereto, the present invention requires a matrix which is responsive to the change in temperature.

The combined teachings of Unger I and Unger II do not lead to a matrix or membrane material which is responsive to a pre-selected physiological parameter (e.g. temperature), whereby to alter the contrast efficacy of a contrast generating species, as disclosed in claim 1. Thus, the present invention is not obvious in view of Unger I and Unger II.

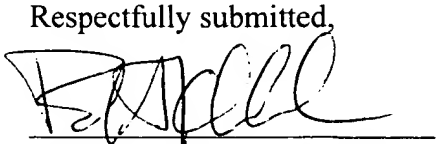
Thus, Applicants respectfully submit that each of the Examiner's rejections under 35 U.S.C. § 103(a) made in the instant application has been overcome and/or obviated and respectfully request that the rejections be withdrawn.

CONCLUSION

In view of the amendments and remarks herein, Applicants believe that each ground for rejection or objection made in the instant application has been successfully overcome or obviated, and that all the pending claims are in condition for allowance. Withdrawal of the Examiner's rejections and objections, and allowance of the current application are respectfully requested.

The Examiner is invited to telephone the undersigned in order to resolve any issues that might arise and to promote the efficient examination of the current application.

Respectfully submitted,



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